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ORIGINAL ARTICLE

Effect of isoflavone consumptions on the recurrence and survival rate among breast cancer patients: an evidence-based case report

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Abstract

Background: isoflavones possess both anti-estrogenic and estrogenic-like properties. Many traditional dishes from Indonesia are rich in isoflavones, such as tempeh, tofu, and soymilk. It remains controversial whether women diagnosed with breast cancer should be advised to avoid or increase the intake of isoflavone food to improve survival.

Objective: to identify the association between post cancer diagnosis isoflavone food consumption with the recurrence and survival rate among women with breast cancer.

Methods: the search was conducted with advanced searching on *PubMed, Cochrane, Scopus,* and *ProQuest* according to the clinical question. The screening of title and abstract using inclusion and exclusion criteria, double filter, and reading full text led to six useful articles. The selected studies were critically appraised for validity, importance, and applicability.

Results: five prospective cohort studies and one meta-analysis were found with comparable validity. Women at the high level of isoflavone intake (>10 mg/day) had a significant reduction in the risk of recurrence and mortality of breast cancer.

Conclusion: isoflavone food intake is associated with better survival, low recurrence, and low mortality among both ER-positive and ER-negative breast cancer patients.

Keywords isoflavone, breast cancer, prognosis, survival

Introduction

Breast cancer is the most common malignancy affecting women, and its incidence and mortality rate is increasing worldwide. The prevalence of breast cancer in Asian countries, including Indonesia has been rapidly increasing during the past few decades.[1] Migration studies have shown that breast cancer incidence in Asian women becomes similar to that of Western women because of westernization diet. The GLOBOCAN study in 2018 reported for 17% of new cases and 11% of mortality rate of breast cancer each year.[2] The number of women who develop breast cancer is more than two times the number of women who die of breast cancer, and this is thought to be related to the relatively high survival rate. Therefore, breast cancer survivors are expected to improve their quality of life through optimal nutrition.

Isoflavones show both anti-estrogenic and estrogenic-like properties. In Asian countries, the average daily intake of isoflavones is 25–50 mg, while in the United States and Europe is less than 3 mg.[3] Isoflavone has been suggested to inhibit breast

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cancer development by decreasing estrogen production and inhibiting cell proliferation.[4, 5] However, isoflavones may exert an estrogenic effect by binding to estrogen receptors in the breast and enhance cellular proliferation.[4, 6] As a consequence, clinicians frequently suggest women with breast cancer to either avoid isoflavone foods entirely or use them in moderation. Isoflavone containing foods are easily found in Indonesia, such as tempeh and tofu.[7, 8] Consumption of that product is high because of the high nutritional value, easy preparation, and affordable price. Tempeh is contained the highest amount of total isoflavone (daidzein and genistein) compared to other soy products.[7]

Data on the association of post-diagnosis isoflavone food consumption with breast cancer prognosis are still conflicting. Experimental studies suggest that isoflavones may interact with tamoxifen therapy, with some studies showing a potential benefit of combined dietary isoflavone intake and tamoxifen use on the inhibition of breast cancer growth, whereas other studies have reported a reduction in the anti-cancer effects of tamoxifen on breast tissue.[6, 9, 10] A concern has been raised whether women should be advised to avoid or increase intake of isoflavone food to inhibit cancer progression. Therefore, we conducted the evidence-based case report to critically evaluate the effect of isoflavones food consumption on the recurrence and mortality rate among women with breast cancer from different ethnicities.

Clinical question

A-52 years old woman admitted to the clinic after being referred by an oncologist with a decrease in food intake and three kilograms of weight loss within one month. She was diagnosed with stage IIIB breast cancer six months ago and had undergone a right radical breast mastectomy and chemotherapy. The patient was malnourished. Previously, she liked to consume tempeh or tofu until the doctor advised her to avoid intake of isoflavone foods (tempeh, tofu, or soybeans) to inhibit her breast cancer progression.

In women with breast cancer, does consumption of isoflavone foods cause a higher risk of breast cancer recurrence or increase mortality?

Methods

A search of literature was done on March, 15st 2020 in four databases including Pubmed, Cochrane, Scopus, and ProQuest using terminology listed in Table 1. The results obtained from four sites were screened by title and abstracts using inclusion and exclusion criteria, double filter, and checked for full-text availability. Eligible articles were cohort prospective, meta-analyses, and systematic reviews that point breast cancer prognosis (recurrence, survival, and mortality rate) as the primary outcome. Review articles were excluded. The search strategy, inclusion-exclusion criteria, and results shown in Figure 1. After article selection, a critical appraisal was done by two authors using guidance for prognostic study from the Center of Evidence-Based Medicine.

Results

Following the search strategy, six original articles were eligible for this evidence-based case report. Two of them (Zhang YF et al., 2012 and Kang HB et al., 2012) were from China; three studies (Caan BJ et al., 2011; Nechuta et al., 2012; and Zhang F et al., 2017) from US, Canada, and Australia; also one meta-analyses among Asian-American women (Chi et al., 2013). Characteristic for stratification, determinant, and results are available in Table 2. The critical appraisal is shown in Table 3. Five articles were cohort prospective with a level of evidence 2 and one article was meta-analysis by Chi and colleagues with a level of evidence 1. All studies considered to have good validity, although the study groups of Zhang, et al.[5] were not similar. The groups were clearly defined and had an adequate follow-up time. From the aspect of importance and applicability, all studies had a relative risk (RR) below 1, which means that higher consumption of isoflavone foods did not increase the risk of recurrence and mortality rate among women with breast cancer.

Discussion

Soybean is rich in isoflavones, which are phytoestrogens with potent anticancer effects.[11] Isoflavones possess anti-estrogenic and

nonhormonal properties that enable them to inhibit the development of breast cancer by decreasing estrogen production, inhibiting cell proliferation, and reducing reactive oxygen species (ROS).[5] Furthermore, isoflavones have anti-angiogenic, activation of natural killer (NK) cells, and antioxidants effects.[1] Experimental studies suggest that isoflavones may interact with tamoxifen, with some studies showing a potential benefit of combined dietary isoflavone and tamoxifen therapy on the inhibition of breast tumor growth.[6, 12] Several reports indicate that the occurrence of breast cancer is considerably lower in Asian individuals compared with other populations because of high levels of isoflavones as part of their regular diet.[3]

Controversy regarding the implementation of dietary isoflavones for breast cancer patients is still debatable. Other than anti-estrogen activity, isoflavones may have estrogen-like properties including the ability to bind to estrogen receptor (ER) in the breast and stimulate cellular proliferation.[6] Taylor et al.[13] showed that isoflavones may enhance the proliferation of breast cancer cells in-vitro. Therefore, clinicians frequently suggest breast cancer patients to avoid isoflavone foods, especially in women with estrogen-sensitive breast cancer. The three isoflavones (genistein, daidzein, and glycitein) account for approximately 50%, 40%, and 10%, respectively, of the total isoflavone content. Each of them has different ER binding affinities and genistein is considered to be the most potent.[14] Genistein has been shown to enhance the proliferation of breast cancer cells in vitro; specifically in ER-positive and promote estrogen-dependent mammary tumor growth in animal studies.[15, 16]

Critical appraisal of six literatures shows no increase in recurrence or mortality among breast cancer patients with high isoflavones consumption. Otherwise, several studies indicate significantly lower risk of recurrence, metastasis, development of new breast cancer, and mortality with high isoflavones consumption.[5, 6, 10, 17, 18] This association was observed across all ethnics groups. A prospective study conducted by Shu et al.[15] showed that Asian women who continued to consume soy after being diagnosed with breast cancer had significantly lower levels of recurrence compared with women who consumed little to no soy. Likewise, a report by Guha and colleagues in 1954 Californian female breast cancer survivors found a trend for a reduced risk of cancer recurrence with increasing quintiles of daidzein and glycetin intake among postmenopausal women (p=0.08 for daidzein, p=0.06 for glycetin).[19] In analyses stratified by ER status; tamoxifen therapy; and menopausal status, we found the inverse association of isoflavone intake with recurrence and mortality appeared among all women with breast cancer. Only one study, Can et al.[4] showed the non-statistically significant reduction of mortality rate among breast cancer women with consumption of isoflavones >16.3 mg/day. Furthermore, there were no negative effects from consumption of isoflavones >35 mg/day or equivalent to the average consumption in Asia.

Isoflavones are usually present in the form of glycosides in soy foods. Isoflavones glycosides have a complex structure, it needs biochemical processes to simplify the structure so it will easily absorb. After being ingested, isoflavones are hydrolyzed to aglycones and carbohydrates by β-glucosidase and other enzymes in the lower small intestine.[7] Aglycones are absorbed from the intestinal tract by the actions of intestinal bacteria. Therefore, inter-individual variability in isoflavone metabolism might be depending on intestinal flora.[10] Daidzein can be further metabolized to dihydrodaidzein, equol, and O-desmethylangolensin which has a higher biological activity compounds.[1, 7] However, individual differences exist in this conversion ability, depending on ethnicity, lifestyle, and genetic polymorphisms.[1, 6]

Traditional soy foods contain approximately 3.5 mg of isoflavones per gram of protein and highly processed soy can lose as much as 80% of its isoflavone content. On average, traditional soy foods contain 20-30 mg of isoflavones per serving (e.g 250 mL of soymilk made from whole soybeans or 100-gram tofu or 75-gram tempeh).[14] Asian diet is rich in soy products. Isoflavones are present in a variety of soy foods but significantly higher amounts are found in tempeh. Tempeh is a traditional fermented product, which often used *Rhizopus oligosporus, R. microsporus,* or *R. oryzae* for its fermentation. Fawwaz, et al.[20] show that genistein level in tempeh is 5 times higher compared with soymilk. That finding proves that the fermentation process can

release sugar on isoflavones to produce genistein. The content of daidzein and genistein in tempeh will increase with 3 days fermentation process. After the third day, the growth in the amounts of aglycones was not statistically important. Generally, depending on the strain, the content of genistein in the fermented product was 8-10 times higher than in unfermented product and the fermentation process will increase their bioavailability.[7]

Isoflavones show a competitive role with endogenous estrogens in estrogen binding receptors. This would increase the synthesis of sex hormone-binding globulin (thus lowering the biological availability of sex hormones), inhibit 17β-hydroxysteroid dehydrogenases (thus reducing estrogen synthesis), and increase clearance of steroids from the circulation. This anti-estrogenic effect may play a positive role in better breast cancer outcomes.[18] Another speculation that the positive result of breast cancer recurrence is dependent on differential gene expression induced by the isoflavones.[16] In our case report, the high intake of isoflavones was positively associated with a better prognosis, which was in line with the previous hypothesis.

Several studies in this case report have examined the effect of soy intake with stratification by ER but reported different findings. The possible anticarcinogenic effect of isoflavones comes from their anti-estrogenic or estrogenic activity mediated by their affinity for ER. However, isoflavones can exert hormonal and anti-estrogenic effects in many ways independently of the ER, and thus further studies are needed to elucidate the underlying mechanism.[18] Tamoxifen is an anti-estrogen widely prescribed to women with ER-positive tumors as long-term adjuvant therapy to prevent recurrences. Experimental studies suggest that isoflavones may interact with tamoxifen therapy with inconsistent findings.[18] In this case report, we did not identify any bad effects on recurrence and mortality for those breast cancer patients who use tamoxifen.

Conclusions

In conclusion, some studies showed that dietary intake of isoflavone is safe and was associated with lower recurrence and mortality among both ER-positive and ER-negative breast cancer patients. However, it required further studies to ensure its interaction with anti-cancer therapy. The results of the study could be applied in Indonesia because most studies include Asian ethnic breast cancer women as subjects. Research showing that approximately 10 mg/day of isoflavones is required to inhibit breast cancer recurrence. Breast cancer patients may beneficially advise to consume one portion of isoflavone foods (e.g 75 g tempeh, 100 g tofu, or 250 mL soy milk each day) and avoiding high processing methods.

Table 1. Terminology used in four database

Database	Terminology	Hits	Results
Pubmed	((((((((isoflavone [MeSH Terms]) OR isoflavone [Title/Abstract]) OR tempeh[MeSH Terms]) OR tempeh[Title/Abstract]) AND ((((((((breast cancer[MeSH Terms]) OR breast cancer[Title/Abstract]) OR breast neoplasm[MeSH Terms]) OR breast neoplasm[Title/Abstract]) OR breast carcinoma[MeSH Terms]) OR breast carcinoma[Title/Abstract]) AND (((((surviv*[MeSH Terms]) OR surviv*[Title/Abstract]) OR prognos*[MeSH Terms]) OR prognos*[Title/Abstract]) Filters: Free full text; published last 10 years; Humans; English	38	3
Cochrane	#1 MeSH descriptor = isoflavone OR tempeh, N= 758 #2 MeSH descriptor = breast cancer OR breast neoplasm OR breast carcinoma, N= 36064 #3 MeSH descriptor = survival OR prognosis, N=121186 #4 = #1 AND #2 AND #3, N= 9	7	2
Scopus	***TITLE-ABS-KEY ("isoflavone" OR "tempeh" AND "breast cancer" OR "breast neoplasm" OR "breast carcinoma" AND "survival" OR "prognosis") AND (LIMIT-TO (ACCESSTYPE(OA))) AND (LIMIT TO (PUBSTAGE , "final")) AND (LIMIT TO (DOCTYPE, "ar")) AND (LIMIT TO (SUBJAREA, "MEDI")) AND (LIMIT-TO (LANGUAGE, "English"))***	23	4
ProQuest	***ab (isoflavone OR tempeh) AND ab("breast cancer" OR "breast neoplasm" OR "breast carcinoma") AND ab(prognosis OR survival)***	15	1

Table 2. Design and results of the selected articles

Articles, year	Stratification analysis	Determinant	Results
Caan. BJ et al 2011	Analyses stratified by: 1. ER/PR status (ER+/PR+ ER−/PR−) 2. Tamoxifen use (yes or no)	A second breast cancer event (local and distant recurrences and new breast primaries) and all-cause of mortality	- Isoflavone intake was unrelated to the risk of a second breast cancer event overall (0.78; 95% CI: 0.46-1.31) or within strata of women defined by hormone receptor status or tamoxifen therapy. - The risk of death tended to be lower as isoflavone intake increased. Women at the highest level of isoflavone intake (>16.3 mg/day) had a non-significant 54% reduction in risk of death compared with the lowest quintile (0.46; 95% CI:0.2-1.05, P for trend= 0.02).
Kang. HB et al 2012	Analyses not stratified by menopausal status, ER/PR status, and tamoxifen use	Survival time which calculated from the date of diagnosis to the date of last follow-up from any causes and cancer-specific death	- The highest soy isoflavone intake (>35.3 mg/day) was associated with a decreased death risk of breast cancer (OR= 0.25, 95% CI: 0.09-0.54).
Nechuta. SJ et al 2012	Analyses stratified by: 1. Menopausal status (pre and postmenopausal) 2. ER status (ER+ or ER−) 3. Tamoxifen use in ER+ breast cancer (yes or no)	Total mortality, breast cancer-specific mortality, and recurrences (or metastasis or development of new breast cancer)	- Consumption of ≥10 mg isoflavone/day was associated with a significantly reduced risk of recurrence (HR: 0.75; 95% CI: 0.61-0.92) but a non-significantly reduced risk of all-cause and breast cancer-specific mortality. The inverse association appeared to be stronger among postmenopausal, ER− and tamoxifen use. - In China, consumption of ≥10 mg/day was associated with a marginally significant reduced risk of recurrence compared with < 4 mg/day (HR: 0.59; 95% CI: 0.47-1.01; p= 0.06), while in the US the reduction was significant (HR: 0.76; 95% CI: 0.58-0.99). -
Zhang. YF et al 2012	Analyses stratified by ER status (ER+ or ER−)	Survival time which was determined from the time of biopsy proven diagnosis to cancer-specific death	- The average intake of soy isoflavone >17.32 mg/day was associated with reduced breast cancer-specific death (HR: 0.64; 95% CI: 0.45-0.93) and the trend of survival was increased with the increasing dosage of soy isoflavone. Better prognosis of breast cancer was found among women with ER+ breast cancer (HR: 0.59; 95% CI: 0.40-0.93) -
Chi et al 2013	Analyses stratified by: 1. ER status (ER+ or ER−) 2. Menopausal status ((pre and postmenopausal) 3. Tamoxifen use	Recurrence and mortality in breast cancer patient	- Soy isoflavone intake >17.32 mg/day was associated with reduced mortality compared with <7.56 mg/day (HR: 0.64; 95% CI: 0.45-0.92), especially in ER−, ER+, premenopausal, postmenopausal, and patients with tamoxifen. - - Soy isoflavones were associated with reduced recurrences at consumption >10 mg/day compared with <4 mg/day (HR: 0.74; 95% CI: 0.59-0.92). The highest soy foods intake after diagnosis was associated with reduced recurrence (HR: 0.74, 95%CI: 0.64-0.85) compared with the lowest intake, especially in ER− and postmenopausal or patients with tamoxifen. -

Table 2. Design and results of the selected articles (continued)

Articles, year	Stratification analysis	Determinant	Results
Zhang. FF, et al 2017	Analyses stratified by: 1. Tumor hormone receptor status (ER+PR+, ER+PR−, ER−PR+ and ER−PR−) 2. Hormonal therapy 3. Race/ ethnicity (non-hispanic white, blacks, hispanics, Asians) 4. Menopausal status (pre and post)	All cause of mortality	- Women in the highest quartile of isoflavone intake (≥1.5 mg/day) had a 21% decrease in all-cause mortality compared to women in the lowest quartile (<0.3 mg/day) (Q4 vs. Q1: HR: 0.79, 95% CI: 0.64-0.97) - In stratified analyses, reduced risk of all-cause mortality associated with high isoflavone intake was statistically significant for women with ER−/PR− tumors (HR:0.49, 95% CI: 0.29-0.83) and women who did not receive hormonal therapy (HR:0.68, 95% CI: 0.51-0.91)

CI= confidence interval; ER= estrogen receptor; PR= progesteron receptor; HR= hazard ratio; mg= miligram; OR= odds ratio; Q= quartile

Table.3 Critical apprisal of the six studies based on criteria by Center of Evidence-Based Medicine, Oxford University

Articles	Validity								Level of Evidence*
	Common point	Follow up	Outcome	Adjustment	Outcome over time	Precision	Applicability	Clinically important	
Caan.BJ et al	+	+	+	+	-	+	+	+	2
Kang.HB et al	+	+	+	+	+	+	+	+	2
Nechuta.SJ et al	+	+	+	+	-	+	+	+	2
Zhang.YF et al	+	+	+	+	-	?	+	+	2
Chi et al	+	+	+	+	-	?	+	+	1
Zhang.FF et al	-	+	+	+	-	+	?	+	2

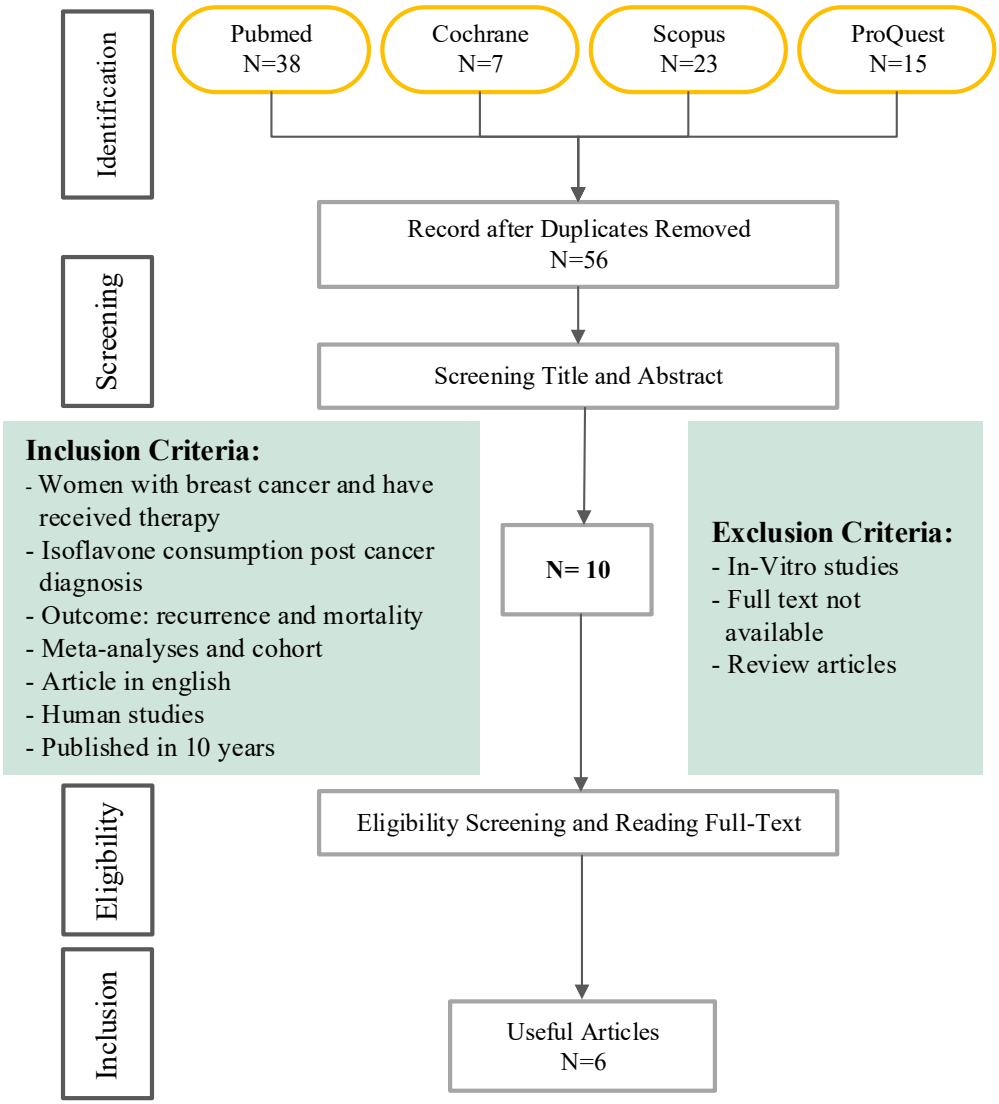

Figure 1. Flowchart of search strategy

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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